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Early sympathetic neural responses during a cold pressor test linked to pain perception

Mu Huang^{1,2}, Jeung-Ki Yoo^{1,3}, Abigail S.L. Stickford^{1,4}, Jonathan P. Moore^{1,5}, Joseph M. Hendrix^{1,6},
Craig G. Crandall^{1,3}, Qi Fu^{1,3}

¹Institute for Exercise and Environmental Medicine, Texas Health Presbyterian Hospital Dallas;

²Department of Health Care Sciences, University of Texas Southwestern Medical Center,
Dallas;

³Department of Internal Medicine, University of Texas Southwestern Medical Center, Dallas;

⁴Department of Health and Exercise Science, Appalachian State University;

⁵School of Sport, Health and Exercise Sciences, Bangor University;

⁶Department of Anesthesiology & Pain Management, University of Texas Southwestern
Medical Center, Dallas.

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Corresponding author: Qi Fu, M.D., Ph.D.,

UT Southwestern Medical Center

Institute for Exercise and Environmental Medicine

Texas Health Presbyterian Hospital Dallas

7232 Greenville Avenue, Suites 435, Dallas, Texas 75231

Phone: (214) 345-8125; Fax: (214) 345-4618

Email: QiFu@TexasHealth.org

Running Title: Pain perception and initial sympathetic responses

24 **Abstract**

25 **Purpose:** There is considerable interindividual variability in the perception of pain. Given that pain
26 management is a major public health problem, gaining insight into underlying physiology of these
27 perceptual differences is important. We tested the hypothesis that when interindividual variability in
28 initial muscle sympathetic nerve activity (MSNA) responses to a cold pressor test (CPT) is
29 identified, the divergent responses will be linked to differences in pain perception in healthy young
30 men and women.

31 **Methods:** In the supine position, blood pressure (BP) and MSNA were measured at baseline and
32 during a 2-minute CPT. Immediately following the CPT, pain was rated (range 0-10).

33 **Results:** Two groups were established: positive responders (Pos, n=12) and negative responders
34 (Neg, n=12) based on the initial (first 30 s) MSNA response profiles (Pos:12±9, Neg:-3±3
35 bursts/min, $P<0.0001$). MSNA response profiles throughout the CPT were different between
36 groups ($P<0.0001$). Peak MSNA increases were different (Pos:27±11, Neg:9±5 bursts/min,
37 $P<0.0001$) and corresponded with initial MSNA responses ($R^2=0.6881$, $P<0.0001$). Blood pressure
38 responses were also different throughout the CPT ($P<0.0001$). Most importantly, the perception of
39 pain induced by the CPT was different between the two partitioned groups (Pos:8±1, Neg:4±1,
40 $P<0.0001$).

41 **Conclusions:** The results indicate that in healthy young men and women, there are divergent
42 initial sympathetic neural responses to a given painful stimulus that are linked to the magnitude of
43 pain perception. These findings highlight the distinctive sympathetic patterns that may contribute to
44 the considerable interindividual variability in the perception of pain.

Key Words: Pain; Blood Pressure; Muscle Sympathetic Nerve Activity; Individual Differences

Introduction

Pain is a major public health problem, with more than 100 million American adults experiencing chronic pain conditions and costing society at least 560-635 billion dollars annually to treat and manage (27). The pathophysiology and subsequent experience of pain is highly complex and results in substantial variability in its perception (36, 58). One of many factors that may modulate the responses to and perception of pain is the health of the cardiovascular system (45). In fact, the systems modulating pain and blood pressure (BP) appear to be inherently linked (6, 23, 43, 44). This is demonstrated in several recent observational studies suggesting that a relationship exists between pain responses and the risk of cardiovascular disease (7, 19, 25).

Acute pain leads to a rapid rise in BP, which in turn may reveal both short- and long term cardiovascular risk (9, 34, 35, 50, 57). Experimentally, inducing noxious stimuli such as strong pressure in the nail, mechanical pressure on the skin, hypertonic saline injection in the skin and muscle, and immersion of the hand in ice water (cold pressor test, CPT), leads to the activation of the sympathetic nervous system via a somatosensory reflex. The subsequent increase in efferent sympathetic outflow (muscle sympathetic nerve activity (MSNA)), evokes downstream cardiovascular responses and an elevation in BP (8, 30, 40, 41, 57). Effectively, experimentally-induced pain allows for a functional model to demonstrate the strong relationship between sympathetically-driven cardiovascular changes and the perception of pain (47).

Very much like the considerable interindividual variability in the perception of pain (20, 47), there is interindividual variability in efferent sympathetic outflow during established sympathoexcitatory stimuli. Indeed, it has recently been demonstrated that during mental stress and hand grip, interindividual differences exist in the MSNA response (18, 26). Particularly

interesting, MSNA response variability during mental stress was apparent even in the initial 30 s of the stress, wherein individuals exhibited either a rise or fall in sympathetic activity (26). Early studies evaluating MSNA observed initial sympathoinhibition responses to noxious stimuli, including the CPT (14, 30, 47). Adaptation to pain is composed of both inhibitory and facilitatory influences (6, 38); however, it is unclear how the initial, individual MSNA responses relate to subjective perception of pain.

Thus, the primary objective of this study is to determine if distinct MSNA response patterns are linked with differences in the perception of pain. Based on the previous studies (30, 33, 47), we hypothesized that there would be substantial interindividual variability in initial sympathetic neural responses to CPT-induced acute pain. We further hypothesized that the initial MSNA responses would correspond to the peak MSNA, BP responses, and perception of pain. Understanding this relationship may set the foundation for future research on chronic pain as well as pain-induced changes related to cardiovascular health.

Methods

Ethical Approval

All participants were informed of the purpose, procedures, and risks of the study before providing written informed consent. The protocol and consent were approved by the Institutional Review Boards at the University of Texas Southwestern Medical Center and Texas Health Presbyterian Hospital Dallas (IRB # STU092013-036, STU082016-057, STU092017-068). This research study conformed to standards set by the Declaration of Helsinki, except for registration in a database.

Subjects

Twenty-four healthy subjects (14 women and 10 men; 32 ± 9 [mean \pm SD] years old, body mass index [BMI]: 26 ± 3 kg/m²) participated. Descriptive characteristics of the subjects are outlined in **Table 1**. All subjects were normotensive and had no evidence of cardiopulmonary, neurological or renal disease, based on history and physical examination at the time of the study. No subject smoked, used recreational drugs, or had other significant medical problems. No woman was pregnant during the experiment. Parental history of hypertension was obtained in each subject.

Measurements

Cardiovascular Variables

Heart rate (HR) was determined from lead II of the electrocardiogram (ECG) (Hewlett-Packard). Arm BP was measured by electrospgymomanometry (model 4240, Suntech); with a microphone placed over the brachial artery to detect Korotkoff sounds. Mean arterial pressure (MAP) was calculated as $[(SBP-DBP)/3] + DBP$, where SBP and DBP are systolic and diastolic BP, respectively. Respiration was monitored by a nasal cannula (Criticare systems, model 602-11).

Muscle Sympathetic Nerve Activity

Multiunit MSNA signals were obtained utilizing the microneurographic technique (55). Briefly, a recording electrode was placed either in the peroneal nerve ($n=19$) at the popliteal fossa or the radial nerve at the spiral groove ($n=5$), and a reference electrode was placed subcutaneously 2 to 3 cm from the recording electrode (12, 39, 59). The nerve signals were amplified (gain 70,000 to 160,000), band-pass filtered (700 to 2,000 Hz), full-wave rectified, and integrated with a resistance-capacitance circuit – time constant 0.1 second (662C-3, Bioengineering of University of Iowa). Criteria for adequate MSNA recording included the following: (1) pulse synchrony; (2) facilitation during the hypotensive phase of the Valsalva maneuver, and suppression during the hypertensive overshoot after release; (3) increases in response to breath holding; and (4) insensitivity to a gentle skin touch or a loud shout (55).

115 *Protocol*

116 The experiment was performed ≥ 2 h after a light meal and ≥ 12 h after the last caffeinated
117 or alcoholic beverage was consumed in a quiet, environmentally controlled laboratory with an
118 ambient temperature of about 25°C. Women were studied during the mid-luteal phase of the
119 menstrual cycle (19-22 days after the onset of menstruation when both estrogen and progesterone
120 are high) or during the high-hormone phase of oral contraceptive use. A urine pregnancy test was
121 performed prior to each testing to confirm that the women were not pregnant.

122 Participants were studied in the supine position. At least 10 min after an acceptable nerve
123 recording site had been found, baseline MSNA and cardiovascular data were collected for 6 min
124 during spontaneous breathing. After that, the subject performed the CPT, where the hand up to
125 the wrist was immersed in an ice water bath ($<0.1^{\circ}\text{C}$) for 2 min, after which the subject's hand was
126 immediately dried and warmed. The subject was instructed to breathe normally, and avoid breath
127 holding during the hand immersion. MSNA and cardiovascular data were recorded continuously
128 during the CPT. Immediately following the CPT, the subject was asked to rate their perception of
129 pain on a numeric rating scale of 0 to 10, with 0 being no pain and 10 being the worst pain
130 imaginable. The scale accommodates the full range of human pain perceptions from non-painful,
131 discomfort to intensely painful sensations (4, 49).

132 *Data Analysis*

133 Data were sampled at 625 Hz with a commercial data acquisition system (Biopac System,
134 Santa Barbara, CA, USA) and analyzed using LabView Software (National Instruments, Austin, TX,
135 USA). Beat-by-beat HR was calculated from the R-R interval of the ECG. MSNA bursts were
136 identified by a custom-made computer program (11), and confirmed by trained personnel. Burst

frequency was defined as the number of bursts per minute and burst incidence was used to normalize burst frequency per 100 heart beats.

MSNA and cardiovascular data were averaged during supine baseline. During the CPT, data were collected for 2 minutes and averaged for every 30 sec, and MAP was collected every minute. In order to achieve our specific aims, we divided our participants into two groups based on the initial directionality of responses to the CPT. Subjects presenting with an *increase* in MSNA burst frequency during the initial 30-s of the CPT were classified and labeled as positive responders (Pos); and those that presented with *no change or decrease* in MSNA initially were classified and labeled as negative responders (Neg).

Statistical Analysis

All data are expressed as mean \pm standard deviation. A two-way repeated measures ANOVA was utilized to compare the changes in HR, BP, respiratory, and MSNA responses between the two groups of responders. Determined *a Priori*, if a significant interaction was identified, multiple post-hoc comparisons of the changes (peak and/or initial) in responses were performed utilizing t-tests with a Bonferroni adjustment. The perceived pain levels for the positive and negative responders were compared utilizing an unpaired t-test and parental history of hypertension, reported by offspring, was compared using a chi-squared analysis. *P* values <0.05 were considered statistically significant. GraphPad prism 6 (GraphPad Software Inc., La Jolla, CA USA) was utilized to perform the statistical analysis and graphing.

Results

Baseline participant characteristics are presented in **Table 1**. Two groups were established based upon the initial (first 30 s) MSNA response to CPT (Pos: 12 ± 9 , Neg: -3 ± 3 bursts/min, $P < 0.0001$). The two groups did not differ in any characteristic at rest. Representative laboratory

tracings of data acquired during baseline, CPT, and recovery are presented in Figure 1. Time course of changes in MAP, MSNA, HR, and respiratory responses to CPT are presented in Figure 2a, Figure 3, and Figure 5 respectively. A significant interaction was revealed in the analysis of MAP, and MSNA expressed as burst incidence and burst frequency. Post-hoc analysis demonstrated significant differences between the two groups in peak changes in MAP (Figure 2b), as well as initial and peak changes in MSNA (Figure 4). The relationship between the initial changes in MSNA and peak changes in MSNA are presented in Figure 6. Significant differences in the reported perception of pain on a scale of 0 to 10 between the two groups are presented in Figure 7. Finally, a significant difference existed between groups with respect to self-reported parental history of hypertension (Figure 8).

Discussion

The primary objectives of this study were to investigate and classify the initial sympathetic neural response profiles to a CPT and to subsequently compare pain perceptions between the two distinct groups. Four important findings were revealed. First, interindividual variability of initial MSNA responses to a cold pressor test was apparent in this study. The patterns of these initial MSNA responses permitted for the classification and comparison of positive and negative responders. Secondly, the stratification of these two groups revealed differences in MSNA and BP response profiles throughout the cold pressor stimulus. In this regard, the initial phase (first 30 s) of the sympathetic response to a CPT (first 30 seconds) corresponds to peak changes in MSNA during the CPT, with positive responders showing greater peak sympathetic responsiveness than negative responders. Third, differences in perception of pain between these two groups were discovered. Specifically, individuals with positive responses during the initial phase of CPT had greater pain scores compared to those with negative responses. Finally, individuals in the initial negative response group to CPT also reported a higher prevalence of parental hypertension. Taken together, these findings provide important insight into the efferent neural underpinnings

185 between the relationship of cardiovascular and pain regulatory systems when exposed to a
186 noxious stimulus.

187 The relationship between blood pressure, MSNA, and pain perception in the current study
188 is consistent with previous investigations. This pattern of cardiovascular and sympathetic neural
189 responses to painful stimuli first emerged in a study by Schobel et al in 1996 (47). In normotensive
190 male subjects, their data showed strong correlations between pain ratings and increases in blood
191 pressure and MSNA in response to pain evoked by mechanostimulation, i.e. skin pinching. Our
192 investigation extends these findings, providing additional evidence that the magnitude of change in
193 blood pressure and MSNA correspond with ratings of pain in response to an alternative painful
194 stimulus (i.e. CPT). Furthermore, in our study, this relationship between blood pressure, MSNA,
195 and pain perception in response to a CPT was demonstrated in a sample that included both
196 normotensive men and women. Individual differences in sympathetic nerve activity and
197 cardiovascular responses to a painful stimulus were also described by Fazalbhoy et al in 2012
198 (20). Variable levels of saline were intramuscularly infused to induce consistent subject ratings of
199 tonic muscle pain; again, distinctly divergent patterns in MSNA, blood pressure and heart rate were
200 observed. In the current investigation, similar divergent MSNA and BP responses were identified
201 under conditions of a consistent noxious stimulus, as opposed to a consistent subjective
202 experience. It is possible that the baroreflex was involved in the initial sympathoinhibition in the
203 negative responders.

204 The highly subjective nature of the pain experience may also be influenced by the intricate
205 interplay between the peripheral and central nervous system. The observed initial divergence in
206 the MSNA responses to CPT in our two groups may be explained by alterations of the peripheral
207 nociceptors (e.g., changes in receptor density and/or sensitivity), modulations within the central
208 nervous system (CNS), or both. While the absolute magnitude of CPT stimulus was consistent
209 across participants, differences in the propagation of the stimulus by sensory afferents may alter

the sympathetic, cardiovascular, and/or perceptual responses. Furthermore, CNS modulation encompasses transmissions of spinal cord inhibitory inter-neurons, cortical processing of nociceptive inputs, and facilitatory/inhibitory descending pain control mechanisms (32, 61, 62). Thus, another explanation underpinning the difference in pain perception intensities between the groups may be attributed to the brainstem's descending modulatory network—both its pro- and antinociception (54). Previous research has demonstrated that CPT-induced pain activates the autonomic nervous system, potentially resulting in hypoalgesia, a response driven by hypothalamic-pituitary-adrenal axis stress reactivity (24, 31, 46, 48) and/or baroreflex-mediated pain-modulation (17). Clinically relevant, CPT-induced hypoalgesia is absent in patients with chronic pain (42). Ultimately, parsing out the exact cause of the different response patterns is beyond the scope of this investigation; rather, these findings reflect the final efferent arc of the summation of all facilitatory and inhibitory mechanisms of pain processing. Future research should take a more mechanistic approach towards understanding the distinct MSNA response patterns described in the current investigation. A potential avenue to further examine physiological mechanisms underlying the CPT response in healthy individuals is to selectively alter pain perception via pharmacologic manipulation. Importantly, extending this research into pathophysiological processes, i.e. maladaptive pain, may give important insight into the management of chronic pain.

The implications of the observed differences in parental history of hypertension between the two groups are unclear. Nearly four decades of research have demonstrated a consistent relationship between hypertension and reduced pain sensitivity (6, 22, 45). In fact, similar to the results of the current study, a handful of investigations have demonstrated reduced cardiovascular responsiveness to acute pain in normotensives with a family history of hypertension (1, 2, 5, 13, 15, 21, 51). However, in stark contrast, an abundance of literature describes an exaggerated or hyper-reactive pressor responses to CPT in hypertensive and pre-hypertensive individuals (3, 10,

28, 37, 53, 60, 63). Furthermore, there are inherent limitations in assessing parental history of hypertension with self-reports, including lack of details (e.g., age of onset, maternal vs paternal) and the tendency for underdiagnosis. Combined with the limited sample size of this study, the most conservative interpretation of this data would be to consider the responses to CPT and parental history of hypertension a spurious relationship that requires further investigation.

Clinically, the results of this study serve as a basis for further investigation into the relationship between sympathetic neural activity and pain regulation. The identification of variability in the neurophysiological components of normal, adaptive pain processing allows for the logical progression to proceed with this type of experimentation in abnormal, pathological pain processing. For example, examining the overlap of the pathological states of these two systems, i.e. cardiovascular dysfunction and maladaptive pain, with the methodology used in this study, would provide clinically relevant data. For instance, alterations in the sympathetic nervous system have been reported in complex regional pain syndrome (29). Additional investigation into direct recordings of sympathetic nerve activity during stress may better elucidate the contributions of the sympathetically mediated pain in this and other chronic pain pathologies. With the current push by the scientific and medical community for the diagnosis and management of pain based on mechanisms, and not symptoms (16, 52, 56); further research using this technique is warranted and may provide specific targets for therapeutic interventions.

Conclusions

The present study reveals interindividual variability in initial sympathetic neural responses to a CPT in healthy men and women. Furthermore, the two divergent initial MSNA response profiles are significantly different in the reported pain to the CPT, as well as peak sympathetic and BP responses. To our knowledge, this is the first study to find these distinctive MSNA patterns, especially initially, and link them to pain perception. The mechanisms responsible for the

interindividual variability in MSNA and how it relates to pain process and hereditary risk of hypertension remains unclear and requires further investigation. Regardless, this study provides clear evidence that pain perception is tightly tied to neurophysiological responses during a noxious stimulus, which may have important clinical implications.

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None of the authors have any financial or personal conflict of interest to disclose.

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Figure Legends

Figure 1: Representative laboratory recordings during baseline, CPT, and recovery from (Panel A) a positive responder and (Panel B) a negative responder.

Figure 2: Panel A) Time course of the changes in mean arterial pressure (MAP) in the positive and negative responder groups during the CPT. Panel B) Group and individual summary data showing peak changes from baseline in MAP in the positive and negative responder groups during the CPT.

Figure 3: Time course of the changes in MSNA in the positive and negative responder groups during the CPT presented as burst frequency (Panel A) and burst incidence (Panel B).

Figure 4: Group and individual summary data depicting initial (first 30 s) and peak MSNA changes from baseline in the positive and negative responder groups during CPT. Panel A and B demonstrates initial and peak changes in MSNA presented as burst incidence (BI). Panel C and D demonstrates initial and peak changes in MSNA presented as burst frequency (BF).

Figure 5: Time course of the changes in HR (Panel A) and respiratory rate (Panel B) in the positive and negative responder groups during the CPT.

Figure 6: Relationship between the initial MSNA and peak MSNA changes during the CPT.

Figure 7: Group and individual summary data depicting differences in reported pain levels during the CPT.

Figure 8: Differences in self reports of parental history of hypertension between the high and low pain groups.

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474 **Figure 1, B.**

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513 **Figure 8.**

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Table 1. Baseline participant characteristics

	Initial Negative Response (n=12)	Initial Positive Response (n=12)	<i>P-value</i>
Female	n=8	n=6	
Race	Asian 1, Caucasian 11	Asian 1, Caucasian 11	
Age (yrs)	30 ± 11	33 ± 7	0.37
BMI (kg/m ²)	26 ± 4	25 ± 3	0.46
Heart Rate (bpm)	61 ± 12	60 ± 16	0.82
SBP (mmHg)	117 ± 18	116 ± 29	0.96
DBP (mmHg)	70 ± 9	67 ± 19	0.51
MAP (mmHg)	85 ± 10	84 ± 21	0.68
Respiration rate (breaths/min)	14 ± 5	14 ± 5	0.79
MSNA BF (bursts/min)	12 ± 8	9 ± 6	0.48
MSNA BI (bursts/100 heartbeats)	19 ± 15	15 ± 9	0.41

Data are expressed as mean ± SD. BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; MSNA, muscle sympathetic nerve activity; BF, burst frequency; BI, burst incidence.